

### **REMARKS**

The Office Action dated June 9, 2010 states that claims 187-188, 191-196, 198-200, 202-205, 208-213, 215-217, 219-221, 223-229, 231-232 and 235-236 are under examination at the present time. Claims 224-236 are canceled herein.

Claims 194 and 229 are rejected as indefinite for lack of antecedent basis for "said carrier" and "said mammal," respectively. These claims have been amended as to dependency. Applicant therefore requests withdrawal of this rejection.

Claims 187-188, 192-193, 195-196, 200, 202-205, 209-210, 212-213, 217, 219-221, 223-226, 228 and 235-236 are rejected as anticipated by Turischev, Farmatsiya, 1996, previously of record, as evidenced by Mann, U.S. Patent No. 6,030,948, also previously of record. The Office has given as a reason for the maintenance of this rejection that the present specification does not provide any specific definition for wound repair or wound healing and that therefore there is no basis for differentiating between wound repair and wound healing. The Office has cited an on-line lay-person's English dictionary which assertedly defines healing as repair.

First, the dictionary chosen by the Office is a computer dictionary designed for lay persons. The Office is required to construe claim terms in the manner a person of ordinary skill in the art would do (not as a lay person), in the context of the specification's teachings as a whole. A definition from an on-line general dictionary is no basis upon which to construe claims in this art. Second, the Office refers to the second definition, which does not relate to physical wounds but to social situations, i.e. repair of relationships between persons. This definition clearly is irrelevant to this art. Persons of skill know that "wound healing" refers to closure of a wound and formation of a scar whereas "wound repair and regeneration," which is claimed here, refers to a process where missing or damaged tissue is replaced with new tissue, tissue that is vascularized and functional. Scar tissue is not vascularized or functional. Thus, "healing" and "repair and regeneration" are not the same thing to a person of skill. In

the absence of any evidence to the contrary, the Office has no basis to deny the differences of these two processes.

The Turischev reference clearly refers to healing and not tissue regeneration, because the author there studied the formation of a scar. See translation, page 3, line 11. Further, the translation from Russian cannot be expected to exactly mimic the use of terms of art unless the translation was prepared by a person of ordinary skill in the art of wound repair.

Applicant here has amended the claims to recite a composition containing a wound repairing and regenerating effective amount of a wound repairing and regenerating polypeptide consisting essentially of thymosin beta (TB)4 or a TB4 isoform that comprises LKKTET (SEQ ID NO:1). Applicant submits that this amendment further distinguishes the claims from the composition used in Turischev. Turischev disclosed thymosin fraction 5, which is a cocktail of numerous active peptides and is known to be functionally complex and different from the single peptide, thymosin  $\beta$ 4. Since thymosin fraction 5 is well-known in the art to contain many different activities and thus to be materially different and to have differences in its basic character from thymosin  $\beta$ 4, claims written with the transitional phrase "consists essentially of" are distinct from the teachings of Turischev.

For these reasons, and the reasons discussed in the previous response, which is re-incorporated here, Applicant requests that the Office withdraw this rejection.

Claims 187-188, 192-193, 195-196, 200, 202-205, 209-210, 212-213, 217, 219-220, 223-226, 228-229 and 235-236 are rejected as anticipated by Mann, U.S. Patent No. 6,030,948, previously of record. The rejection is made with respect to 35 U.S.C. § 102(e). Mann teaches thymosin fraction 5, which the Office asserts meets the limitation of "claim 3." The present application does not contain a claim 3, and the third claim (claim 189) is withdrawn and not rejected here.

Independent claim 187 has been amended to recite a composition containing a wound repairing and regenerating effective amount of a wound repairing and regenerating polypeptide consisting essentially of thymosin beta (TB)4 or a TB4

isoform, as distinguished from the multi-active cocktail composition of thymosin fraction 5. Mann teaches only thymosin fraction 5. Therefore the rejection has been overcome since Mann does not teach to use a composition containing a wound repairing and regenerating polypeptide which consists essentially of TB4 or a TB4 isomer.

Furthermore, as explained several times, Mann does not teach applying thymosin fraction 5 to a wound, for any purpose, much less wound healing, and certainly not wound repair and regeneration. Since Mann obviously does not teach explicitly that one should produce wounds on the scalp to treat alopecia caused by fungus, the Office is relying on a purported inherent teaching of doing so by instructing the reader to apply an "acid peel" solution. The Office has misunderstood the doctrine of inherency, which requires the cited reference to teach a method or composition which inevitably and necessarily produces the assertedly inherent effect or teaching. Mann teaches to use a solution containing 2-30 % of a weak acid (see Table 10, col. 13), applied for as little time as one minute (see col. 13, line 27). A skilled person knows that such a treatment does not inevitably or necessarily wound the scalp.

What is more, the Office has produced no evidence whatsoever which even tends to show the asserted inherent disclosure. It is the Office's burden to show that the reference in question contains the inherent disclosure and the Office has failed to do so, or even attempted to do so. Applicant therefore requests that the Office either meet the burden required to make out a case of inherent anticipation, or withdraw the rejection. Applicant repeats and re-incorporates the arguments and evidence previously submitted in this regard here.

Applicant refers the Office to the discussion above with respect to the on-line lay dictionary definition of "healing" which was misapprehended by the Office and is irrelevant to the understanding of the person of skill in the context of this invention. The Office has provided no relevant evidence showing that a person of skill in the art of wound repair and regeneration would understand the term "wound" to encompass exfoliation of dead skin. The Office has merely stated its desired conclusion,

demanded proof that the conclusion is not true, and ignored all evidence to the contrary.

Applicant is entitled to a patent unless the Office can show that the invention is not novel. The Office has not shown this to be the case, but instead falls back on its purported right to give claims the broadest reasonable interpretation by giving them the broadest needed interpretation to make its conclusion, regardless of whether that interpretation is reasonable from the viewpoint of a person of skill.

The Office is taking Applicant's statement that dead skin is caused to peel away as an admission that the live skin is peeled away by the "acid peel" treatment, causing a wound and a need for "regeneration." A person of skill knows what a wound is and that exfoliation of some dead skin (a natural phenomenon that occurs on human skin on a constant basis) does not produce a wound. Peeling away of dead skin does not imply peeling away of skin generally, however much the Office insists, and certainly not producing a wound. If this were the case, all persons would have wounds on every skin-covered surface over the entire body at all times and would be in need of constant medical treatment. Thus, the Office's interpretation of "wound" cannot be seen as reasonable under any circumstances and should be withdrawn.

The Office refers to Table 10 of Mann and the expert opinion of the declaration in a previous declaration as not providing experimental or documentary evidence that the acid peel treatment would have certain properties. Mann also provides no experimental or documentary evidence showing that the acid peel treatment would inevitably produce a wound. Applicant considers this an admission by the Office that there is no experimental or documentary evidence showing the properties of the Mann acid peel. Since there is no evidence, the Office cannot make out a case of anticipation, either expressly or inherently, and the rejection must be withdrawn. Applicant submits, for example, that one could obtain the evidence the Office requests by applying lemon juice (which is about 5-6% citric acid) diluted with equal parts of water to live human skin for one minute, rinsing, and examining the skin for bleeding or other signs of a wound.

Applicant would again like to repeat that causing some dead skin to peel away is not the same as causing the skin itself to peel away as the Office repeatedly insists. See, for example Office Action at page 16, lines 2-3. And it is not the same as causing skin to be peeled away such as by tearing, piercing, cutting or breaking the skin. To assume this from a cosmetic treatment is unreasonable.

The Office also complains that the present claims do not recite "broken skin." They do recite "wound." Applicant urges the Office to construe claims from the viewpoint of a reasonable person of skill, as the law requires. The Office Action can repeat that acid peels cause outer dead layers of skin to peel away dozens of times during prosecution, but repetition does not change the fact that peeling away dead skin in an acid peel does not produce a wound as that term is understood by a person of skill. Applicant requests that the Office withdraw the rejection of claims as anticipated by Mann.

Claims 187-188, 191-196, 198-200, 202-205, 208-213, 215-217, 219-221, 223-229, 231-232 and 235-236 are rejected as obvious over Turischev, discussed previously and above, Mann, discussed previously and above, and Puolakkainen, previously of record. Turischev and Mann refer to thymosin fraction 5, which is a complex mixture of dozens of active peptides, including thymosin  $\alpha$ 1, as the Office admits. These references do not teach that thymosin  $\beta$ 4, or even thymosin fraction 5 has any effect such as claimed here. As discussed previously, neither Turischev nor Mann provide even slightest guidance to substitute thymosin  $\beta$ 4 for the complex group of active peptides in thymosin fraction 5 or hint that thymosin  $\beta$ 4 contains the activity needed for wound repair and regeneration. Further, one of skill would not have a reasonable expectation of success for thymosin  $\beta$ 4 alone, from the teachings of Turischev and/or Mann. Applicant refers to the discussion above concerning other features of the invention that are lacking in Mann, for example treatment of a wound.

Puolakkainen is cited for teachings related to TGF- $\beta$  and does not add anything to the art that, when combined with Turischev and Mann, would guide the skilled reader to use thymosin  $\beta$ 4 and TGF- $\beta$ . Thus, even the combined references do not teach the

elements. Further, there is no motivation or guidance that would lead a skilled artisan to substitute the individual peptide thymosin  $\beta$ 4 for the active cocktail thymosin fraction 5 with any reasonable expectation of success, with or without further addition of TGF- $\beta$ .

The Office cannot make out a prima facie case of obviousness with respect to the amended claims. Therefore, Applicant requests withdrawal of the rejection.

Claims 187-188, 191-196, 200, 202-205, 208-213, 217, 219-221, 223-229 and 235-236 are rejected as obvious over Malinda, Baumann, and Biotech Patent News, all previously of record. None of these references contain any teaching with respect to wound repair and regeneration.

Biotech Patent News is a news report and not a peer-reviewed journal respected by persons of skill. It is not relevant to the understanding of persons of skill. Furthermore, this reference reports on a study to be conducted in the future and says absolutely nothing about the results which were obtained or even the results one might reasonably expect to obtain. This reference is completely irrelevant to the claims here for the above reasons and because the future study relates to wound healing and not wound repair and regeneration.

Malinda is cited for teachings related to endothelial cell chemoattractant, cell migration, wound closure speed and angiogenesis. The Office concedes that Malinda does not teach using TB4 for wound healing but presents arguments designed to persuade that it would have been obvious to try using TB4 for such a purpose. The factors mentioned are positive results in an in vitro wound "scratch" model, which in no way correlates with effects in vivo in wound healing, much less in wound repair and regeneration. The Malinda "wound closure" assays were done with endothelial cells to test their migratory activity. These cells do not regenerate a wound. In fact, Malinda shows that fibroblasts do not migrate in the Boyden chamber assay, so any skilled artisan noting from Malinda that endothelial cells but not fibroblasts migrate in response to TB4 would be discouraged from using TB4 for wound healing or wound repair and regeneration in vivo. The Office's remark that motivation to use the method in vivo is found because Malinda reported "positive results for in vitro studies" is misleading. The

results were positive for cell migration of one cell type, not for tissue repair or regeneration. Therefore, if one were motivated, it could not be for the claimed method.

Baumann is cited for teaching that in vitro "wound healing" is increased by TB4. These teachings, alone or in combination with Malinda, do not suggest to the skilled artisan that he should attempt the claimed method for promoting wound repair or regeneration or that thymosin beta 4 could reasonably be expected to possess the recited activities. The Office is straining to make out a case that one would have been motivated to try TB4 for wound healing, but cannot show a reasonable expectation of success for wound repair and regeneration with this combination of art. There is no hint or guidance in the art toward wound repair or regeneration. Applicant therefore requests that the Office consider the amended claims and withdraw this rejection.

In combination, therefore, the art cited here suggests that endothelial cells but not fibroblasts migrate in response to thymosin  $\beta$ 4 (Malinda), that in vitro wound healing (migration) of unknown cell types is influenced by thymosin  $\beta$ 4 (Baumann), and that workers plan to study whether thymosin  $\beta$ 4 has any in vivo wound healing effects (Biotech Patent News). This does not add up to the specific guidance required under current standards to make out a prima facie case of obviousness to all of the recited claim elements. One of skill recognizes that in vitro results based on one cell type do not provide a reasonable expectation of success for the complex in vivo process of wound repair and regeneration. The Office therefore cannot make out a prima facie case of obviousness here. Applicant requests the rejection be withdrawn.

Claims 187-188, 191-196, 198-200, 202-205, 208-213, 215-217, 219-221, 223-229, 231-232 and 235-236 are rejected as obvious over the combination of the three references cited above, with the addition of Puolakkainen, also of record. The content and relevance of the Malinda, Baumann and Biotech News references are discussed above. Puolakkainen is cited only for the additional teaching that TGF-beta enhances wound healing. This reference does not add anything to the combination discussed above in terms of a reasonable expectation of success for any wound healing application or in terms of the invention claimed here, which is a method of wound repair

and regeneration. The references do not teach or fairly suggest a method of wound repair and regeneration, the specific method of wound repair and regeneration claimed here, or provide any reasonable chance of success for such a method.

Applicant requests withdrawal of this rejection.

Claims 187-188, 191-196, 200, 202-205, 208-213, 217, 219-221, 223-229, and 235-236 are rejected as obvious over Mann, previously of record. Mann does not teach a method of promoting wound healing or wound repair and regeneration, does not teach administering a composition to a subject in need of wound healing or wound repair and regeneration, does not teach a wound-repairing and regenerating-effective amount of thymosin  $\beta$ 4 and does not even mention, suggest, or hint at wounds at all, or inherently disclose wounding for the reasons discussed above and in previous responses. There is nothing in the reference that guides the artisan to believe that thymosin  $\beta$ 4 could possibly assist in wound repair or regeneration.

Under current standards of obviousness law, the Office must provide an articulable reason why the cited art reference specifically guides the skilled person to what is claimed. Here, the Office has made conclusory statements based on fabricated facts. This is not sufficient. There is no express or inherent teaching or suggestion concerning wounds in Mann. Unless and until the Office can provide some showing of this asserted inherent teaching or a suggestion that guides the reader to wound repair and regeneration, the Office has no basis upon which to reject the claims presented here over Mann. The rejection should be withdrawn.

The Office here has taken the position, in general, that the claims here are anticipated and/or obvious until Applicants can conclusively prove that they are not, even in the face of asserted "facts" set forth by the Office. Patent law, however, places the burden on the Office to show in the first instance that Applicant is not entitled to a patent. For example, at this stage the Office appears to be requiring Applicant to prove that the prior art does not teach in vivo wound repair and regeneration even though the Office has not presented any evidence that it does and in some respects has even admitted that there is no evidence that it does teach or suggest the claims. Also, the



Office appears to require Applicant to prove that the art is not enabling for things not even mentioned in the art, such as in vivo wound repair and regeneration. Further, the Office requests Applicant to disprove predictability of results of a study which had not even taken place when the cited news report was published. The art cited here simply does not teach or suggest what the Office claims it does. The Office's assertion that Puolakkainen and Biotech Patent News do not discourage wound treatments, for example, does not indicate that they do teach or suggest wound treatments. The Patent Office may not prove a thing by stating that the reference does not prove the opposite, but this is what the Office is doing here, and then requiring the Applicant to prove in some way that the reference does teach the opposite in order to overcome the rejection. This approach is contrary to patent law and practice and contrary to logical reason.

It is the Office's burden to make a showing of the facts alleged to render the claims unpatentable. Merely stating unshown facts and conclusions does not make out a case for anticipation or obviousness. The Office has unfairly placed the initial burden of proof on Applicant by requiring Applicant to disprove its unfounded conclusions. Applicant therefore requests that the Office withdraw the rejections here or provide a factual showing upon which the conclusions of unpatentability can be based reasonably.

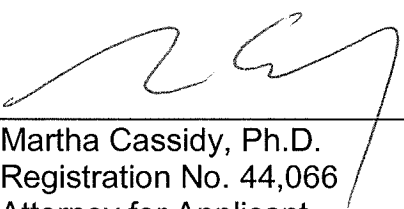
Applicant requests that the Office review the cited art for what it actually teaches and reasonably and fairly suggests to a person of skill in the art, and reviewing whether it is able to meet any standard of making out a prima facie case, based on facts and reasons, that the claims as amended here are unpatentable.

The Office has maintained a rejection of claims 187-188, 191-193, 195-196, 198-200, 202-205, 208-210, 212-213, 215-217, 219-220, 223-225, 231-232 and 235-236 under doctrine of non-statutory double patenting over claims in three separate pending patent applications. Since the applications have not been patented, the rejections are provisional. Applicant continues to request that all provisional rejections on grounds of double patenting be held in abeyance until such claims have been indicated to be

allowable otherwise and it becomes possible to determine whether claims directed to the same invention or an obvious variant thereof would be issued in more than one patent.

Applicant requests reconsideration of the application and allowance of all claims presented herein.

Respectfully submitted,

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